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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,209	01/16/2001	James E. Hildreth	JHU1290-7	5480

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EXAMINER
NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
1645	18

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/761,209	Hildreth
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *8, 9, 11-17, and 24-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *8, 9, 11-17, and 24-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Additionally Applicants amendment filed July 21, 2003 (Paper Number 17) has been received and entered. Claims 25-34 have been added, consequently claims 8-9, 11-17 and 24-34 are pending in the instant application.

Claim Rejections - 35 USC § 112

1. The rejection of claim 24 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Additionally this rejection is applied to newly added claims 25-28.

Applicants are asserting that the specification discloses that antibodies encompassed within the claimed methods can inhibit HIV-mediated syncytium formation in culture (page 21, line 18 to page 22, line 20 and page 24, lines 11-15). Applicants conclude that the specification discloses a means by which HIV can spread among cells in a subject is prevented using such

antibodies. Applicants further point to Exhibits A-C, which show on-going trials which provide objective evidence that those skilled in the art believe that immunotherapy can be useful for treating HIV infection. Applicants finally assert that the skilled clinician would know measures of clinical benefit typically used for monitoring the particular recited disorders.

Applicants arguments have been fully considered but are not found to be fully persuasive.

Facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. See In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988). The Federal Circuit has noted, however, that only those factors that are relevant based on the facts need to be addressed. See Enzo Biochem. Inc. v. Calgene, Inc. 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir 1999).

First, no working examples are present. Second, the prior art describes a number of concerns and failures pertaining to the development of immunotherapy for the amelioration of HIV. Fahey et al (Clin. Exp. Immunol. Vol. 88, pp 1-5, 1992) in which a summary of the results obtained in trials using numerous different types of immune-based therapies have not achieved success. (See table 1). This clearly demonstrates points 4 and 5 above, the nature of the

invention is in an extremely difficult field for achieving success, and this art demonstrates the failure of others in this exact field. Consequently, one of skill in the art would be forced into excessive experimentation to practice the broadly claimed invention.

Applicant's further point to Exhibits A-C to support the position that those skilled in the art believe that passive immunotherapy can be useful for treating AIDS. However, the exhibits cited by Applicants are currently ongoing, whereas the filing date of the instant application is June 1989 and therefore the exhibits are not an enabling disclosure at the time of the instant application. (See In re Glass 181 USPQ 31 (CCPA 1974). Furthermore, Applicant's cited Exhibit B is merely a study to determine the safety of a human monoclonal antibody. No demonstration of the amelioration of HIV is presented. Furthermore, Exhibit C is a study of the combination of immunotherapy and anti retroviral therapy. This is simply not commensurate in scope with Applicants claims which recite solely immunotherapy. As set forth previously, Fahey et al have characterized the lack of efficacy of immunotherapy in ameliorating HIV.

Applicants finally assert that the skilled clinician would know measures of clinical benefit typically used for monitoring the particular recited disorders. However, while measures of clinical benefit can be ascertained, the art as set forth by Fahey et al has shown numerous failures of the same immuno-based therapy in which no clinical benefit was afforded against HIV infection.

The claims are directed to methods of ameliorating an immune response mediated disorder in an animal wherein the disorder is AIDS, autoimmune disease, and graft rejection.

Applicant's specification contains insufficient guidance to one of skill in the art for the treatment of AIDS, autoimmune disease and graft rejection. The specification provides no description of critical parameters for administering antibodies in order to achieve a desired therapeutic outcome. General protocols for effective antibody-based treatment of AIDS, autoimmune disease, and graft rejection have not yet been established in the art. The specification does not describe what, if any, clinical changes or benefits are manifested as the result of monoclonal antibody-mediated individuals suffering from AIDS, autoimmune diseases or graft rejection such that one of skill in the art could determine the efficacy of the claimed invention. Undue experimentation would be required of one of skill in the art to practice the claimed methods relying only on the teachings of the instant specification for guidance in view of the current state of the art to which the invention pertains.

The obstacles to the development of therapeutic approaches with regard to the treatment of HIV-1 infection in humans are well documented in the scientific literature. Theses obstacles include the fact that the modes of viral transmission include virus-infected mononuclear cells which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, the existence of a latent form of the virus, the ability of the HIV-1 virus to hide in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus due to the blood-brain barrier, and the complexity and variation of the elaboration of the disease. The status of immunobased therapies in HIV infection and AIDS is summarized in a review article by Fahey *et al* (Clin. Exp. Immunol. Vol 88, pp 1-5, 1992), cited of interest, Fahey

et al teach that clinical benefit in trials using different approaches to immune-based therapies have not achieved a great deal of success. Table 1 on page 2 summarizes the results obtained in trials using numerous different types of immune-based therapies and teaches that antibody-based therapies involving the administration of immune serum gamma globulin or murine anti-gp160 monoclonal antibodies did not achieve clinical change or benefit. In view of the lack of working examples, and the lack of success which has been achieved to date in the use of immune-based therapies in general, and of antibody-based therapies in particular, for therapy of HIV-1 infection, one of skill in the art would be forced into undue experimentation to practice the broadly claimed invention.

For reasons of record in Paper Number 12, as well as the reasons set forth above this rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. The rejection of claims 8-9, 11, and 13-15 under 35 U.S.C. 102(e) as being anticipated by Arfors is maintained. Additionally, this rejection is applied to newly added claims 24-27, 29-32 and 34.

Applicants are asserting that the claims have been amended to recite only autoimmune disease, graft rejection, or AIDS, and that Arfors does not teach of any of these specific conditions.

Applicants arguments have been fully considered but are not found to be fully persuasive.

Applicants arguments are not found to be fully persuasive in view of the disclosure of Arfors.

Arfors (US Patent Number 4,797,277) disclose of methods for reperfusion therapy of a mammalian organ comprising the step of administering systemically to said organ a therapeutically active amount of an antibody preparation having specificity for a LAC-epitope that is responsible for leukocyte-endothelial cell adherence. (See claims). Arfors further sets forth that "the invention is primarily concerned with the treatment of humans, although organs dissected from humans and reperfused may be subjected to the invention." (See column 3, lines 27-30). Arfors further sets forth of reperfusion-induced tissue damage occurring in clinical conditions such as "organ transplantation." (See column 1, lines 15-20).

Given that organ transplantation is a graft, the antibodies having specificity for a leukocyte adhesion receptor β-chain when administered to inhibit reperfusion damage in an organ transplantation as disclosed by Arfors would inherently ameliorate graft rejection. This is deemed

to be an inherent characteristic in view of antibodies reacting with the same epitope being given in the same amount to a patient with a graft in both the instantly filed invention and the disclosure of Arfors.

The claims are directed to a method of ameliorating an autoimmune disease or graft rejection in an animal which comprises: administering to the animal a therapeutically effective amount of an antibody, capable of suppressing intercellular leukocyte adhesion, wherein the antibody binds to an epitope on the leukocyte adhesion receptor β-chain, thereby ameliorating the autoimmune disease or graft rejection in the animal.

Arfors (U.S. Patent Number 4,797,277) disclose of a method for treating mammalian organs suffering from ischemia in order to prevent ischemia/reperfusion-induced tissue damage, which involves administering anti LAR-β chain-specific monoclonal antibody 60.3. (See column 2). The examples describe parenteral administration at a dose within the range specified in claim 15.

For reasons of record in Paper Number 12, as well as the reasons set forth above this rejection is maintained.

3. The rejection of claim 8 under 35 U.S.C. 102(b) as being anticipated by Vedder *et al* is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The rejection of claims 8-9, 11 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Arfors or Vedder *et al* in view of Springer *et al* is withdrawn.

5. The rejection of claims 8-9, and 11-15 under 35 U.S.C. 103(a) as being unpatentable over Arfors, Vedder *et al* and Springer *et al* and further in view of Hildreth *et al* is withdrawn.

6. The rejection of claims 8-9, 11-17 and 24-34 under 35 U.S.C. 103(a) as being unpatentable over Arfors in view of Springer *et* al, Hildreth *et al* and Pastan *et al* is maintained.

Applicants are asserting that none of the cited references teaches or suggests ameliorating AIDS, an autoimmune disease, or graft rejection.

However, as set forth above in paragraph 2, Arfors contemplates treatment of organ transplantation in column 1 and 3.

It would have been *prima facie* obvious to combine the teachings of the cited prior art and to produce conjugates comprising anti-LAR-β chain specific monoclonal antibodies and cytotoxic

moieties and to use such conjugates in methods for treating autoimmune diseases and organ transplantation. One of ordinary skill in the art would have been motivated to do so in view of the combined teachings of Pastan *et al*, Arfors *et al*, and Springer *et al* showing success of reducing injury in organ transplantation individuals.

Double Patenting

7. The rejection of claims 8-9, 11-17 and 24-34 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,888,508 is maintained.

It is noted that Applicant's have indicated a willingness to file a terminal disclaimer upon the indication of allowable subject matter. However until a terminal disclaimer is made of record this rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

August 27, 2003